## REMARKS

Claims 1-13 and 21 are pending. The claims are have been amended to recite methods of alleviating back pain by administering into the intervertebral disc space specific types of glutamate receptor antagonists. Administration to disc tissue/space permits storage of medication in larger amounts, allowing the antagonist to diffuse continuously from the disc to the epidural space over a period of several weeks rather than a few days without the need for implantation of a pump in humans.

No new matter has been added by this amendment.

***Claim Rejections--35 U.S.C.§ 112***

Claims 1-5, 9, 11-13, and 21 were rejected for failing to comply with the enablement requirement. Due to the existence of "different types of glutamate receptors, NMDA, non-NMDA, kainite, AMPA and mGluR (ionotropic and metabotropic)", the Examiner stated "the entire scope of the instant claims is not enabled". In the paragraph spanning pages 4-5 of the Office Action, the Examiner states:

> Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Even if the mechanism is defined for a particular class of drugs it is not predictable from such studies that each drug that falls into the class will be useful in treating the condition without any severe adverse or side effects. Applicants' claim administration of glutamate receptor antagonists in a method of alleviating back pain. The claims are very broad with respect to the glutamate receptor antagonist compounds known and yet to be discovered.

To address the Examiner's overbreadth rejection, Applicants have amended claim 1 to require a KA receptor antagonist, a NMDA receptor antagonist, or an AMPA receptor antagonist.

With respect to predictability, Applicants have tested compounds belonging to each class of receptor antagonist in an art-recognized rat animal model for pain (see accompanying Declaration of Dr. Harrington). The results using exemplary compounds from each class of antagonist confirm the data described in the specification of the above-referenced patent application and demonstrate predictability of the claimed methods.

***Claim Rejections--35 U.S.C.§ 103***

Claims 1-5, 9, 12, 13, 21 were rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682). According to the Examiner, the NewsRx reference teaches that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation, rather than pressure on nerves caused by the herniation and the Zhuo reference teaches glutamate as a sensory transmitter for pain and further teaches that antagonism of both kainate and AMPA receptors (glutamate receptors) yields greater analgesic effects in adult animals than AMPA receptor antagonism alone. The Examiner concludes,

> It would have been obvious to one having ordinary skill in the art at the time of the invention from the above cited prior art teachings that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation and administration of glutamate receptor antagonists would be useful in treating pain including back pain.
>
> Ausman et al. teaches a method of relieving back pain and related symptoms comprising injecting drugs into an intervertebral disk of the back (see abstract, claims). It would have been obvious to one having ordinary skill in the art at the time of the invention to have injected drugs into an intervertebral disk tissue because Ausman teaches it is a common and successful procedure to inject effective dosages of drugs into an intervertebral disk of the back to relieve pain.

The Ausman reference describes and claims administration of an aqueous solution of cysteine into the intervertebral disk of the back and reports that this composition is better than the older methods of administration of chymopapain, because the risk of allergic reaction and anaphylactic shock is reduced. None of the prior art references provide any suggestion or motivation to substitute cysteine for another drug, much less a glutamate receptor antagonist. Thus, it appears that the Examiner cites Ausman simply for the premise that drugs can be administered to intervertebral disc tissue. The fact that a prior art reference teaches that medication can be placed into a disc is not sufficient to establish obviousness of the claimed methods. To use that logic, any pharmaceutical that was designed for oral administration would

not be patentable based on the fact that the literature is filled with references to the use of oral medication.

Claims 6, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682) as applied to claims 1-5, 9, 12, 13, 21 above and further in view of Lawand et al. (Euro J of Pharmacology, 324, (1997), 169-177). The Examiner states:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to administer ionotropic glutamate receptor or NMDA type receptor antagonist such as MK-801 or an AMPA receptor antagonist such as CNQX in a method to alleviate back pain in mammal. The motivation to do so is taught by the prior art teachings cited above and Lawland et al. It would have been obvious from the teachings of NewsRx document and Zhou teaches that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation and administration of glutamate receptor antagonists would be useful in treating pain including back pain. Lawland teach that intra-articular injection in knee joint of either an NMDA (MK-801) or a non-NMDA glutamate receptor (CNQX) attenuated the thermal hyperalgesia and the mechanical allodynia produced by glutamate. Hence one of ordinary skill in the art would have been motivated to administer such compounds to alleviate back pain by inhibition of binding of free glutamate released to alleviate back pain.

The Lawland reference, the disclosure of which is limited to knees, was apparently cited for the description of specific compounds. In the interview with the Examiner in May of 2009, the Examiner acknowledged that cartilage in knee, hip, elbow and spine are quite different and that experiments on knees would not allow assumption of the same antinociceptive effects elsewhere in the body, because aggrecan and extracellular free glutamate levels in these different joints have never been compared or suggested to be similar. Lawland demonstrates evidence for the presence of glutamatergic neurons and antinociceptive effects of an NMDA antagonist in the knee but demonstrates no evidence for elevated extracellular levels of glutamate in tissues other than the knee. Without such evidence or suggestion, one cannot extrapolate that glutamate exudes from damaged knee cartilage or other cartilage as it does from damaged disc. Nor does the literature suggest that there are any glutamatergic neurons in the disc. Moreover, the Lawland article suggested that glutamate concentration did not affect pain, reporting that injection of Glu into the knee joint cavity led to some behavioral changes but the changes were not seen at higher concentrations (p. 171, col. 2, of Lawland) and demonstrating that knee pain is

different than sciatic pain. The lack of literature supporting the likeness of knees and discs and the lack of literature on the presence of glutamatergic neurons in the disc literature undermines and in fact dismantles this ground of rejection.

None of the prior art references suggests injecting a glutamate receptor antagonist into the intervertebral disc tissue to relieve pain from the disc or surrounding structures. For that matter, nor has any investigator has ever injected glutamate into the disc space to create pain. Cartilage from knees, hips and spines is structurally and biochemically different. The claims are based on demonstration of high extracellular glutamate concentration within the disc space and data demonstrating sensitivity of the sciatic nerves to the presence of extracellular glutamate receptor antagonists. Prior to the invention, the disc has never been contemplated as a site for intervention to reduce pain related to glutamate concentrations. The combination of references cited above fails to describe or suggest the methods of the amended claims.

Claims 8, 11 were rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682) as applied to claims 1-5, 9, 12, 13, 21 above and further in view of Stanfa et al. (Neuroscience, 1999, vol. 93, No. 4, p 1391-1398). Regarding the contribution of the Stanfa reference, the Examiner states:

> Stanfa et al. teaches the enhanced role of AMPA and Kainate antagonists in spinal nociceptive processing in inflammatory states. Hence one of ordinary skill in the art would have been motivated to administer a KA receptor antagonist compound such as LY383884 to alleviate back pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Stanfa is limited to intrathecal administration. This reference fails to contribute any disclosure suggesting administration of the recited antagonists to intervertebral disc tissue.

Claim10 was rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682) as applied to claims 1-5, 9, 12, 13, 21 above and further in view of Garrett ( Biol. Res. for Nursing, Vol. 1, No. 4, Apr 2000). The Garrett reference appears to have been cited only for the description of a specific compound. The Examiner stated:

> Garett teaches the crucial role of excitatory amino acid, glutamate, NMDA and non-NMDA receptors in pain transmission, pain modulation, central sensitization and the

> sensation of hyperalgesia (see Abstract, p 311, col. 1, lines 15-44). The reference further teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia. Hence one of ordinary skill in the art would have been motivated to administer a metabotropic glutamate receptor antagonist such as L-AP3in conditions like degenerated disc to alleviate back pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Garrett contributes no description of route or location to which a therapeutic compound is administered. Therefore, this reference fails to remedy the deficiencies of the earlier cited combination of references.

Applicants submit that the amended claims are non-obvious over the cited combinations of prior art references, because none of the combinations would motivate one of skill in the art of neurosurgery to treat pain as required by the claims. In this case, the disc serves as a medication depot as well as a site of action of the glutamate receptor antagonist. The claims are drawn to the administration of glutamate receptor antagonists into discs for pain associated with glutamate levels in disc material, i.e., back pain and disc herniation pain. Using the disc as a site for treatment with glutamate receptor antagonists or as a medication depot has never been suggested by any of the combinations of references. The rationale for using the disc space to treat back pain and sciatic pain with glutamate receptor antagonists is tested, rational, and unique.

Not only has intervertebral disc administration of glutamate receptor antagonists not been suggested, this route of administration offers unexpected advantages over earlier approaches to pain management. Administration to disc tissue/space permits storage of medication in larger amounts as well as continuous diffusion from the disc to the epidural space over an extended period of time, thereby avoiding implantation of a pump. The addition of metabotropic receptor agonists or antagonists to the disc increases the extent and length of duration of pain relief when placed in the disc space.

In view of these distinctions and advantages, Applicant respectfully requests reconsideration and withdrawal of this rejection.

## CONCLUSION

In view of the foregoing amendments and comments, Applicant requests reconsideration and withdrawal of the rejections. Applicants submit that the application is in condition for allowance, and request a Notice for same. Please charge any fees that may be due, or credit any overpayment of same, to Deposit Account 50-0311, Ref. No. 38591-501001US.

Respectfully submitted,

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